PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
X-14685		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US02/21296	29/07/2002	17/01/2002
International Patent Classification (IPC) or national classification and IPC C07D451/04		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 13 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
10/01/2003	26.03.2003
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wörth, C Telephone No. +49 89 2399 8726

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US02/21296

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-132 as originally filed

Claims, No.:

1-71 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 69 and 71 with respect to IA.

because:

☒ the said international application, or the said claims Nos. 69 and 71 with respect to IA relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☒ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-22,48-56,
	No:	Claims	1-4,23-47,57-71
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-71
Industrial applicability (IA)	Yes:	Claims	1-68, 70
	No:	Claims	

2. Citations and explanations
   see separate sheet

1. **Reference is made to the following documents:**

D1: WO 99 32117 A (SIBIA NEUROSCIENCES INC ;VERNIER JEAN MICHEL (US); MC DONALD IAN A) 1 July 1999 (1999-07-01) cited in the application

D2: WO 97 19059 A (SIBIA NEUROSCIENCES INC ;VERNIER JEAN MICHEL (US); MCDONALD IAN A) 29 May 1997 (1997-05-29) cited in the application

D3: WO 96 37226 A (MENNITI FRANK S ;PFIZER (US); CHENARD BERTRAND L (US)) 28 November 1996 (1996-11-28)

D4: WO 01 19817 A (ABBOTT LAB) 22 March 2001 (2001-03-22)

D5: WO 00 44755 A (ABBOTT LAB) 3 August 2000 (2000-08-03)

D6: ELLIOT R L ET AL: '2-(ARYLOXYMETHYL) AZACYCLIC ANALOGUES AS NOVEL NICOTINIC ACETYLCHOLINE RECEPTOR (NACHR) LIGANDS' BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 6, no. 19, 1996, pages 2283-2288, XP000618280 ISSN: 0960-894X

D7: RADL, STANISLAV ET AL: 'Synthesis and analgesic activity of some side-chain modified anpirtoline derivatives' ARCHIV DER PHARMAZIE (WEINHEIM, GERMANY) (2000), 333(5), 107-112 , XP002219143

D8: KRAISS, G. ET AL: 'Stereospecific methods of forming ethers by nucleophilic reactions of 3.alpha.-substituted tropanes' J. ORG. CHEM. (1968), 33(6), 2601-3 , XP002219144

2. **Section III: Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 69 and 71 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

3. **Section IV: Lack of unity of invention**

The present international application relates to thio-bridged aryl derivatives of formula (I) of claim 1 that are capable of modulating acetylcholine receptors.

The claimed compounds possess

a) a common biological **activity** (*acetylcholine receptor modulators*) and

b) a common **structural** feature being an *(hetero)aryl-S(O)$_r$-bicycle* moiety.

ad a) Document D1 discloses pyridine compounds (see formula (Z) on page 6) falling under the generic definition of present formula (I). In particular, reference is made to page 75, table I, fifth example.

Document D2 discloses certain aryl compounds (see formula (Z) on page 4) falling under the generic definition of present formula (I). In particular, reference is made to page 45, table II, last example.

In order to exclude subject-matter of D1 and D2, a proviso is introduced in present claim 1 excluding certain thio-bridged phenyles or pyridines.

Accordingly, a single general inventive concept based on a common structure of the remaining compounds as special technical feature representing a contribution over the prior art is no longer apparent.

ad b) The compounds disclosed in D1 and D2 have the same biological activity as the subject-matter of the present international application, that is to say are modulators of acetylcholine receptors (see D1, page 5, lines 8-24; see D2, page 2, lines 15-21).

Since the disclaimed compounds (see above) possess acetylcholine receptor modulating activity, a single inventive concept based on a common biological activity of the remaining compounds as special technical feature representing a contribution over the prior art is no longer apparent.

Accordingly, the present international application does not fulfill the requirements set forth in Rule 13(1) PCT.

The subject-matter of the present international application can therefore be divided in the following groups of inventions:

Group 1: subject-matter related to monocyclic aryls of formula (I) wherein X,W,W',Y and Y' are carbon

Group 2: subject-matter related to monocyclic aryls of formula (I) wherein one of X, Y or Y' is nitrogen

Group 3: subject-matter related to monocyclic aryls of formula (I) wherein two of X, W, W', Y and Y' are nitrogen

Group 4: subject-matter related to monocyclic aryls of formula (I) wherein one of W or W' is nitrogen

Group 5: subject-matter related to bicyclic aryls of formulae (Ia) or (1b).

The requirements of unity are not fulfilled.

4. Section V: Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

4.1 Novelty (Art. 33(2) PCT)

4.1a Group 1

The subject-matter of Group 1 differs from

document D1 in view of the **carbocycle** defined by X,W,W',Y and Y'

document D2 in view of the **thio-bridge** (the generic definition of compounds of D2 consists of a compulsory moiety "E" which is absent in the present subject-matter) and the **proviso** of claim 1 (excluding the last example on page 45, table 1)

document D4 in view of the **carbocycle** defined by X,W,W',Y and Y' (see definition of "B" in D4)

document D5 in view of the **bridged** ring system (the corresponding moiety in D5 contains two nitrogen atoms)

document D6 in view of the **thio-bridge**

document D7 in view of the **proviso** of claim 1

document D8 in view of the **proviso** of claim 1

Document D3 discloses in preparations 36 (see page 78), 38 and 39 (see page 79) and 41 (see page 80) thio-bridged aryl which differ from Group 1 in view of the

halogen substituent at position 4 (see definition of present R_2).

The subject-matter of Group 1 fulfills the requirements of Art. 33(2) PCT.

4.1b Group 2

The subject-matter of Group 2 differs from

document D1 in view of the fact that the subject-matter of group 1 is considered as a **purposive selection** over the subject-matter of D1 (see broad definition of "D-E-G" in D1 whereas the present Group 2 relates only to thio-bridged compounds); the overlapping example on page 75, table 1 (5th compound) is excluded by the proviso of claim 1

document D2 in view of the **heteroaromatic** ring

document D3 in view of the **heteroaromatic** ring

document D4 in view of the **bicyclic heteroring**

document D5 in view of the **bridged** ring system (the corresponding moiety in D5 contains two nitrogen atoms)

document D6 in view of the **thio-bridge**

document D7 in view of the **proviso** of claim 1

document D8 in view of the **heteroaromatic** ring

The subject-matter of Group 2 fulfills the requirements of Art. 33(2) PCT.

4.1c Group 3

The subject-matter of Group 3 differs from

documents D2-D4 and D6-D8 in view of the heteroaromatic ring containing **two nitrogen** atoms;

document D5 in view of the **bridged** ring system (the corresponding moiety in D5 contains two nitrogen atoms).

However, the disclosure of document D1 is considered as overlapping with the subject-matter of Group 3. Claim 1 of document D1 discloses compounds (see formula (I)), wherein A and B are independently selected from -N- or -C- with the proviso that one of A and B is nitrogen. Accordingly, the disclosure encompasses compounds with one or two nitrogen atoms. The latter overlaps with the present subject-matter of Group 3.

The subject-matter of Group 3 does not fulfill the requirements of Art. 33(2) PCT.

4.1d Group 4

The subject-matter of Group 4 differs from

document D1 in view of the **meta-position** of the nitrogen atoms vis-à-vis the thio-bridge

document D2 in view of the **heteroaromatic** ring

document D3 in view of the **heteroaromatic** ring

document D4 in view of the **bicyclic heteroring**

document D5 in view of the **bridged** ring system (the corresponding moiety in D5 contains two nitrogen atoms)

document D6 in view of the **thio-bridge**

document D7 in view of the **meta-position** of the nitrogen atoms vis-à-vis the thio-bridge

document D8 in view of the **heteroaromatic** ring

The subject-matter of Group 4 fulfills the requirements of Art. 33(2) PCT.

4.1e Group 5

The subject-matter of Group 5 differs from

documents D1-D4 and D6-D8 in view of the **bicyclic aryl** group

document D5 in view of the **bridged** ring system (the corresponding moiety in D5 contains two nitrogen atoms)

The subject-matter of Group 5 fulfills the requirements of Art. 33(2) PCT.

4.2 Inventive step (Art. 33(3) PCT)

4.2a Group 1

Document D2 is considered as **closest prior art**. This document discloses substituted aryl compounds as modulators of acetylcholine receptors.

In view of this document, the **problem to be solved** can be regarded as the provision of further compounds having the same biological activity as those disclosed in D2.

Starting from document D2, the **solution** consists in a thio-bridge thereby omitting the compulsory group "E" of document D2.

This solution is considered as **obvious** in the light of the disclosures of documents D1 and D4 indicating that the bridging moiety between the aryl part and the (bridged) heterocyclic group does not compulsorily need a group corresponding to "E" of document D2. Document D1 teaches for example that the groups D and G are optionally present. In addition, document D2 discloses itself a strong indication for the fact that "E" is not compulsory in table II, page 45, last compound. This compound is active although it does not contain a group "E". Accordingly, a man skilled in the art would not be surprised to obtain acetylcholine receptor modulators starting from D2 and omitting the group "E". Furthermore, the general statement on page 52, lines 13-15 does not substantiate that the presently claimed compounds do actually solve the given problem and that the claimed breath is substantiated.

The subject-matter of Group 1 does not fulfill the requirements of Art. 33(3) PCT.

4.2b Group 2

Document D1 is considered as **closest prior art**. This document discloses substituted heteroaryl compounds as modulators of acetylcholine receptors.

In view of this document, the **problem to be solved** can be regarded as the provision of further compounds having the same activity as those described in document D1.

The **solution** provided consists in a purposive selection over document D1 in view of the restriction to thio-bridged compounds. Such a selection can only be regarded as inventive, if the compounds present unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of Group 2.

The subject-matter of Group 2 does not fulfill the requirements of Art. 33(3) PCT.

4.2c Group 3

Document D1 is considered as **closest prior art**. This document discloses substituted heteroaryl compounds as modulators of acetylcholine receptors.

In view of this document, the **problem to be solved** can be regarded as the provision of further compounds having the same activity as those described in document D1.

The solution provided consists in pyridazines, pyrimidines and pyrazines representing the same or a different distribution of the nitrogen atoms over the ring starting from document D1.

This solution is considered as obvious. The provision of further heteroaryls containing two nitrogen atoms starting from document D1 disclosing pyrimidines as useful constituents of acetylcholine receptor modulators is merely one of several straightforward possibilities from which a person skilled in the art would select without the excercise of inventive skill in order to solve the problem posed. In particular, the skilled man having knowledge of document D5 would be aware of the fact that the heteroaryl moiety can be varied in the field of acetylcholine receptor ligands (see definition of R_1 in D5)

The subject-matter of Group 3 does not fulfill the requirements of Art. 33(3) PCT.

4.2d Group 4

Document D1 is considered as **closest prior art**. This document discloses pyridines compounds as modulators of acetylcholine receptors.

In view of this document, the **problem to be solved** can be regarded as the provision of further compounds having the same activity as those described in document D1.

The **solution** provided consists in pyridines wherein the nitrogen atom is in meta-position to the thio-bridge.

This solution is considered as obvious. The provision of further pyridines starting from the disclosure of document D1 already disclosing pyridines as useful heteroaryls is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. In particular, the man skilled in the art having knowledge of document D4 would be aware of the fact that in the field of acetylcholine receptor meta-connected pyridines are already used (see e.g. formula II of D4).

Moreover, underlying the principles of structure-activity relationship (SAR), it is stressed that a similar qualitative biological activity can be expected for structurally similar compounds. As a consequence thereof, SAR allows the prediction that for formal analogisations the pharmaceutical activity will be maintained.

Furthermore, the general statement on page 52, lines 13-15 does not substantiate that the presently claimed compounds do actually solve the given problem and that the claimed breath is substantiated.

The subject-matter of Group 4 does not fulfill the requirements of Art. 33(3) PCT.

4.2e Group 5

Document D1 is considered as **closest prior art.** This document discloses substituted heteroaryl compounds as modulators of acetylcholine receptors.

In view of this document, the **problem to be solved** can be regarded as the provision of further compounds having the same activity as those described in document D1.

The **solution** provided consists in compounds containing a bicyclic aromatic group according to formulae (Ia) or (Ib).

This solution is considered as obvious. The provision of bicyclic aromatic moieties in the field of acetylcholine receptor ligands is already known from document D5. It would be obvious to the person skilled in the art, namely when the same result is to

be achieved, to apply the feature of bicyclic aromatic groups with corresponding effect to the bridged systems according to document D1, thereby arriving at compounds according to Group 5. The subject-matter of Group 5 does therefore not involve an inventive step.

Furthermore, the general statement on page 52, lines 13-15 does not substantiate that the presently claimed compounds do actually solve the given problem and that the claimed breath is substantiated.

The subject-matter of Group 5 does not fulfill the requirements of Art. 33(3) PCT.

4.3 Industrial applicability

For the assessment of the present claims 69 and 71 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.